REMARKS

Upon entry of this amendment, claims 1, 2, and 7-25 are pending. Claims 1, 2, and 7-25 were rejected.

In summary, the Examiner rejected all of the pending claims for formal (§ 112) and art based (§§ 102 and 103) reasons, and requested an abstract of the disclosure on a separate page. More specifically, claims were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite, under 35 U.S.C. § 102 for allegedly being anticipated by Griffiths et al. (Methods in Mol. Biol. (1997), Vol. 75, p. 59-75, hereafter "Griffiths") or Davis et al. (Methods in Mol. Viol. (1997), Vol. 75, p. 77-89, hereafter "Davis"), and under 35 U.S.C. § 103 for allegedly being obvious over the combination of Culver et al. (WO 92/10564, hereafter Culver) Wiktor et al. (US 4,664,912, hereafter Wiktor), Pollard (Methods in Mol. Biol. (1997), Vol. 75. p. 1-11, hereafter Pollard), and Norrgren et al. (Exp. Cell. Res. (1984), Vol. 152 p. 427-435, hereafter Norrgren).

Abstract under 37 C.F.R. § 1.72(b)

On page 2 of the Office Action, the Examiner requested an abstract, in accordance with 37 C.F.R. § 1.72(b). Applicant submits the abstract on a separate page.

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FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
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Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-2 and 7-25 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention.

The Examiner has rejected claim 1, stating that the term "a repeated discontinuous process" is confusing. Office Action at page 2. Applicant refers the Examiner to page 3, lines 20-27 of the specification. In sum, the instant invention is directed to a method wherein after growth of a first generation of cells, only a portion of the cells grown are used as the seed population for the next generation of cells. Cells from the remaining portion are "discontinued" from the propagation cycle and are used for experimentation or production of a biological. This method is a "repeated discontinuous process."

Applicant distinguishes a "repeated discontinuous process" from processes in which cell lines are grown up from a working seed, and wherein the entire population of progeny are grown from successive generations to achieve a high volume of cells. In such methods, once a high volume of cells is achieved, then (and, only then) are the cells used for experimentation (e.g., U.S. Patent No. 4,644,912, discussed in the specification at 1, lines 15-25). Such a method is a "continuous process" for growing a large population of cells.

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& DUNNER, L.L.P.
1300 I STREET, N. W.
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The Examiner rejected claim 1, alleging that the claim does not sufficiently define what type of cell is claimed. Applicant argues that in light of the specification, this claim term is clear. The specification specifically says that the invention can be carried out with, although is not limited to,

> "animal cell cultures and more in particular with anchorage dependent cells. Suitable types of cells are e.g. hamster cells (CHO, BHK-1), monkey cells (Vero), bovine cells (MDBK), canine cells (MDCK), human cells (CaCo, A431), or chicken cells (CEF)."

Specification at 5, lines 11-14. These limitations are presently recited in dependent claims 9 and 10. Since the specification clearly defines this term, Applicant contends that it is necessary to amend independent claim 1 to include these limitations.

The Examiner has also rejected claim 1 because the claim allegedly does not sufficiently specify what type of biologicals are claimed. Office Action at page 3. Applicant contends that the term "biological" is specifically defined in the specification as:

> "any substance or organism which can be produced from a cell culture. Examples of "biologicals" are viruses and proteins such as enzymes."

Specification at page 2, lines 34-36. One skilled in the art would fully understand the scope of this term as used in the claims.

The Examiner has argued that the term "a desired cell volume" claimed in claim 1 is vague. Office Action at page 3. Applicant argues that one skilled in the art could readily identify a desired cell volume and manipulate the claimed process using well known art-recognized techniques to achieve the desired cell volume. Furthermore, in

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1300 I STREET, N. W.
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two examples in the specification, Applicant exemplifies different cell volume, i.e., 5 x 10^6 cells/ml (Example 1, page 6, line 8), and 2.8 x 10^6 cells/ml (Example 7, page 9, line 30). Applicant submits that one skilled in the art would not need any more information to select and achieve a specific desired cell volume.

The Examiner has further rejected claim 1 for allegedly being incomplete for omitting what the Examiner has characterized as essential steps, which include:

> "how to set up the scale and the apparatus for the initial cell culture, how to transfer and expend the cell culture in preproduction phase, the step and control strategy for maintaining the micro-environment of the cell culture, such as pH, Oxygen, CO_2 cell viability etc., how to induction [sic] of the biological molecule and harvesting the biological, etc."

Office Action at page 3. Applicant contends that these steps and considerations are well known to those skilled in the art, are of general knowledge, and thus need not be claimed, much less detailed in the specification. For example, the Griffiths reference supplied by the Examiner discusses methods for controlling pH and oxygen levels (at page 60, second paragraph).

The Examiner has rejected claim 11, alleging that the term "substance" is indefinite. Office Action at page 3. Applicant believes the Examiner meant to reject the word "substrate". Applicant contends that the specification clear as to contemplated substrates at page 3, lines 9-10, and in Example 1. In addition, one skilled in the art

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1300 I STREET, N. W.
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would be aware of appropriate substrates. For example, many appropriate substrates are discussed in the cited Griffiths reference (at pages 65-74).

The Examiner has contended that the word "carrier" in claim 14 is vague. Office Action at page 3. Applicant proposes that one skilled in the art, having considered the present claims and supporting specification would be able to identify acceptable carriers. Furthermore, exemplary carriers are discussed at page 5, lines 20-23, of the specification and a micro-carrier is mentioned in Example 1.

The Examiner also rejected claims 19-21 for allegedly being vague and indefinite for using the terms virus, protein and enzyme respectively. As discussed above, Applicant contends that one skilled in the art would be able to readily identify various biologicals about to be produced by the present invention, whether they are virus, a protein or an enzyme. Furthermore, the Examiner has provided no reason as to why any particular viruses, proteins or enzymes would not be capable of being prepared by the present invention. Accordingly, the Examiner's rejection is improper and his request for recitation of a single virus, protein or enzyme is unreasonable and too limiting.

Finally, the Examiner rejected claim 24, alleging that the term "raising temperature" is vague. Applicant also disagrees with the Examiner on this point. As claim 24 is dependent from claim 23, which recites a specific temperature, i.e., 17° to 32° C, Applicants contend that it would be clear to one skilled in the art that claim 24 contemplates the temperature being raised above 32° C to a temperature where the

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cells are revitalized to cell growth. Furthermore, this language is supported in the specification at page 5, lines 6-7, and also in Example 4, where the temperature was raised to 37° degrees C (at page 7, line 20).

For all of these reasons, Applicant respectfully requests that the rejection under § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102(b)

The Examiner also rejected claims 1-2 and 9-22 under 35 U.S.C. § 102(b), as allegedly being anticipated by Griffiths for the reasons stated at pages 4-5 of the Office Action. The Examiner generally states that Griffiths provides examples of methods for scale-up of anchorage-dependent animal cell cultures for producing biologicals. Applicant does not necessarily disagree with this generic characterization of the teachings of Griffiths, however, they fail to see how such teachings anticipate the presently claimed discontinuous method. None of the disclosed scale-up approaches teaches the discontinuous aspect of the present inventive process.

One of the advantageous characteristics of the claimed invention is that it provides "a much faster through-put in preparation of cells of the production of biologicals" than other methods. Specification at page 1, lines 34-35. Because the inventive method calls for experimentation or biological production at every cycle of the process, i.e., each generation of production, the inventor of the instant invention has alleviated the problem of the long time period needed to prepare the cells and the risks

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1300 I STREET, N. W.
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of leaving them in a culture system for long amounts of time found in methods such as that described by Griffiths. Furthermore, the present invention allows for cells that can be frozen for later use, further alleviating the time they would spend in damaging media conditions. Thus, not only does Griffiths not each the presently claimed method, the claimed invention provides a novel improvement over the methods taught by Griffiths. In fact, Griffiths even teaches away from the rapid, large scale production of multiple generations of experimental cells of the claimed invention, stating that one should "not be over-ambitious with regard to scale" (page 60).

The Examiner has also rejected claims 1-2, 9, 11-14, 22 and 24-25 under 35 U.S.C. § 102(b) as allegedly being anticipated by Davis for the reasons stated in the Office Action at page 5. In particular, the Examiner alleges that the Davis system can harvest some of the produced cells and freeze them for later use. At no time, however, does Davis teach a "repeated discontinuous process" as claimed in the present application, wherein a portion of the produced cells of each generational cycle is used as seed cells for the next generation and the other portion is discontinued from the propagative process.

In fact, Davis teaches that the experiment (production) terminates for one of two reasons: loss of productivity or blockage of the flowpath (page 85, last paragraph, and page 86, first sentence under 3.7 heading). This determines the length of the culture according to the teachings of Davis (page 85, last paragraph). In contrast, the instant

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invention teaches repetition of the experiment (production), and the availability of new batches of production cells. Because each and every element of the claimed invention is not taught by Davis, Davis cannot anticipate the claimed invention.

Rejection under 35 U.S.C. § 103

The Examiner has also rejected all the claims under 35 U.S.C. § 103, for being obvious over the combined teachings of Culver, Wiktor, Pollard, and Norrgren for the reasons stated at pages 6-7 of the Office Action. Applicant contends that none of the cited references alone or in combination, as cited by the Examiner, suggest the presently claimed invention. Furthermore, Applicant argues that the Examiner has failed to satisfy his burden of establishing how and why one skilled in the art would be motivated to combine the teachings of the cited art and reasonably expect to achieve the present invention.

None of the cited references disclose the claimed invention, either alone or when considered together. Specifically, none of the cited art teaches or suggests the claimed elements of the "repeated discontinuous process" of producing cells described in the present application.

Culver discloses a method for culturing a high titer of vectors by continually removing the medium from a hollow fiber reactor lined with the vector-producing cells. Culver then replaces the medium containing the vectors with new, fresh media and the

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cycle continues. At no point does Culver teach a discontinuous propagation of cells as taught in the claimed invention, only a continuous production of the biological (the vector). See Culver at page 14, lines 5-10. The biological is the used to transduce target cells in a second bioreactor. In contrast to the instant invention, all of the cells are then harvested, and none are propagated (Culver at page 30, lines 2-7).

As described in the specification at page 1, Wiktor describes a method for preparing a large volume of anchorage-dependent cells beginning with a seed population. However, Wiktor merely teaches that one may successively pass all of the progeny into successively larger bioreactors until an optimum volume is achieved. It is only after several generations of this continuous process that the cells are harvested for their intended use (col. 2, lines 59-67). Applicant argues that such teaching is in stark contrast to the claimed invention, in which cells are removed from the system at every step of the cycling for biological use. Furthermore, this teaching fails to satisfy the deficiencies of Culver.

As described by the Examiner, Pollard provides a discussion of many factors related to culturing cells, including propagating cells from a smaller population of seed cells. However, he only discusses growing cells for one generation, thus this reference does not teach the "repeated discontinuous process" of the instant invention.

Finally, Norrgren merely discloses a primary culture of heart cells grown on Cytodex 3 microcarriers for the large-scale production of embryonic nerve growth

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1300 I STREET, N. W.
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stimulating factors. See Norrgren at pages 427, 431. However, there is no mention of discontinuously propagating the cells as taught in the instant invention. Thus, Applicant contends that the teachings of Norrgren also do not relate to the instant invention.

In sum, Applicant argues that the combined teachings of these references do not and cannot result in the claimed invention, in which cells are removed from the system at every step of the cycling for biological use. As discussed above, none of the cited references teach a repeated discontinuous process of culturing cells to a desired cell volume for use in preparation of a biological as required by the claimed invention.

Finally, the Office has also failed to demonstrate that one skilled in the art would be motivated to combine the Culver, Wiktor, Pollard, and Norrgren references. Even if, *arguendo,* the combined references did provide all of the elements of the instant invention, the Examiner has not shown that the references contain any language regarding the desirability of the combining the references, as taught in the M.P.E.P. § 2143.01, *citing In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Thus, Applicant contends that the disclosure of, motivation, and desirability to make the claimed invention are found only in the instant specification which evidence cannot be used to satisfy the Examiner's burden for establishing a *prima facie* case of obviousness. Therefore, Applicant respectfully requests that this § 103 rejection be withdrawn.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Conclusion

Based on the preceding amendments and remarks, Applicant submits that the application is now in condition for allowance, and such action is earnestly requested.

Please grant any extensions of time required to enter this filing and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Carol P. Einaudi.
Carol P. Einaudi
Reg. No. 32,220

Dated: June 12, 2001

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000